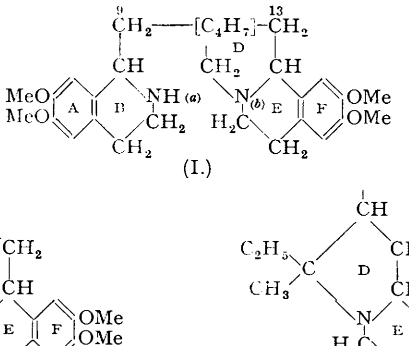
674. *Studies of the Structure of Emetine. Part IV. Elucidation of the Structure of Emetine.*

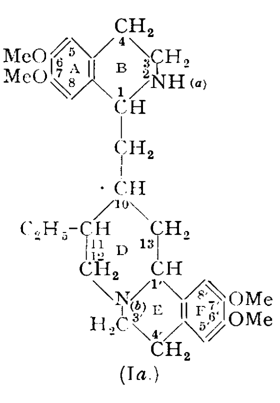
By A. R. Battersby and H. T. Openshaw.

The later stages of the Hofmann degradation of emetine (Part I, this vol., p. 859) have been studied more fully. The course of the oxidation of des-*N*(*a*)-emetinetetrahydromethine (IV) and of *des*-N(a)-*emetinehexahydrobismethine* (VII) shows the absence of side-chains at $C_{(9)}$ and $C_{(13)}$ in emetine (I), thus disproving the structure of Brindley and Pyman (*J.*, 1927, 1067). The final, nitrogen-free product (X) was optically inactive, and on ozonolysis yielded formaldehyde and a ketone, and must therefore be (X*a*), (X*b*), or (X*c*). Dehydrogenation of *des*-N(a)-*emetinehexahydromethine* (VI) gave the *pyridine* base (XIV), which was oxidised to 5-*ethylpyridine*-2 : 4-*dicarboxylic acid* (XV). The structure of emetine is therefore (I*a*).

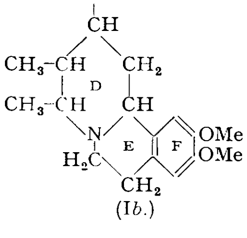
In Part I (*loc. cit.*) we described the degradation of emetine (I) by Hofmann's method to a nitrogen-free product (X). Since the completion of this work, Späth and Pailer (*Monatsh.*, 1948, **78**, 348) have described a similar degradation leading to a crystalline diene (XI). Ozonolysis of (XI) gave an unsaturated aldehyde (XII) which could be oxidised to methyl ethyl ketone and β-(4 : 5-dimethoxy-2-ethylphenyl)propionic acid, and reduced to a saturated aldehyde (XIII). The carbon skeleton of (XIII) is derived from (I) by the removal of N(*a*) and of all the atoms forming rings E and F. By a second degradation, in which N(*b*) and the atoms forming rings A and B were removed, Pailer (*ibid.*, 1948, **79**, 127) again obtained the aldehyde (XIII). These results are compatible only with the structure (XIII*a*) for the aldehyde, and this structure, which has been confirmed synthetically (Pailer, *ibid.*, p. 331), leads to three possible formulæ (I*a*, I*b*, and I*c*) for emetine (Pailer and Porschinski, *ibid.*, 1949, **80**, 94; Battersby, Openshaw, and Wood, *Experientia*, 1949, **5**, 114). Of these three structures, Pailer and Porschinski favour (I*a*), since they have obtained 4-methyl-3-ethylpyridine (β-collidine) by drastic dehydrogenation of two degradation products of emetine. The same structure is favoured by Robinson (*Nature*, 1948, **162**, 524) on biogenetic grounds.



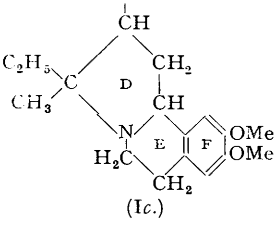
(I.)



(I*a*.)



(I*b*.)



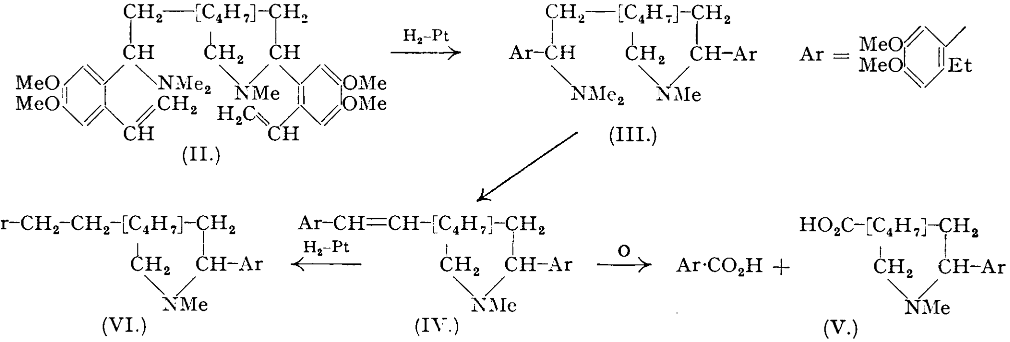
(I*c*.)

In two preliminary communications (Battersby, Openshaw, and Wood, *loc. cit.*; Battersby and Openshaw, *Experientia*, 1949, **5**, 398) we have also advanced experimental evidence which excludes the structures (I*b*) and (I*c*), but confirms the structure (I*a*) for emetine. In the present paper, these investigations are described in detail, and other observations connected with the Hofmann degradation of emetine are recorded. Although in its final stages, our work has been greatly facilitated by the findings of Späth and Pailer, it constitutes an entirely independent proof of the structure of emetine.

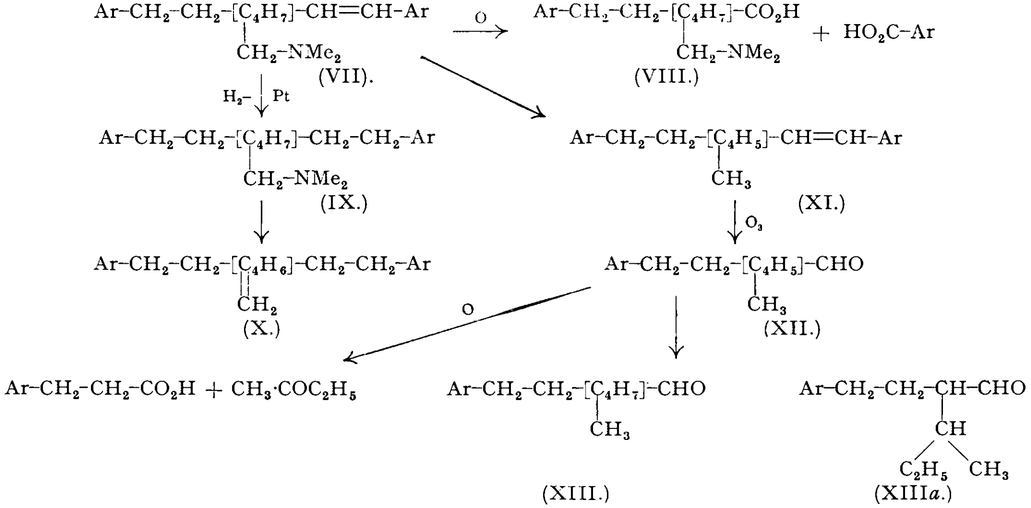
In view of the ready thermal decomposition of the dimethiodide of *N*-methylemetinetetrahydromethine (III) (Part I, *loc. cit.*; Part III, this vol., p. 1174), the stability of the dimethiodide of *N*-methylemetinemethine (II) has been studied. As expected, this substance decomposed readily at 100°, but, apart from a little trimethylamine, no pure product could be isolated.

In Part I we described the oxidation of des-*N*(*a*)-emetinetetrahydromethine (IV) to 6-ethylveratric acid. The second product was an amino-acid (V), which has now been obtained crystalline; analysis of its *ethyl* ester showed that its formation involved no loss of carbon atoms. Hence, (IV) contains the structure Ar–CH=CH– and $C_{(9)}$ in emetine carries two hydrogen atoms.

Hydrogenation of (IV) produced the crystalline base *des*-N(a)-*emetinehexahydromethine* (VI)



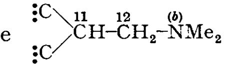
which reacted slowly with methyl iodide to give the methiodide already described (Part I). Hofmann degradation of this methiodide gave rise to *des*-N(a)-*emetinehexahydrobismethine* (VII), purified through its crystalline *picrate*, together with some regenerated (VI) and a little neutral material, apparently a non-conjugated isomer of (XI). The point of ring-fission in this degradation is shown to be between N(*b*) and $C_{(1')}$ by the similarity of the absorption spectrum of (VII) to that of (IV), indicating the presence of the same chromophore, Ar–CH=C<, and by the thermal stability of the methiodide of (VII). Had ring fission occurred at the alternative position N(*b*)–C_{12}, the product would possess a structure of the α-arylalkylamine type, and, similarly to (III) and synthetic models (Part III), would form an unstable methiodide.

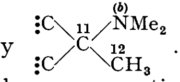


Oxidation of des-*N*(*a*)-emetinehexahydrobismethine (VII) with barium permanganate gave 6-ethylveratric acid and an amorphous amino-acid (VIII). Analysis of the *methyl* ester of (VIII) showed that no loss of carbon had occurred in the oxidation, and hence proved the absence of a side-chain at $C_{(13)}$, in contradiction to the proposed emetine formula of Brindley and Pyman (*loc. cit.*). This oxidation also gives independent confirmation of the presence of a second dimethoxy*iso*quinoline system in emetine.

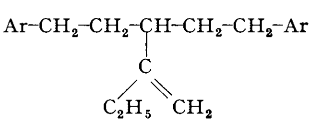
Hofmann degradation of the methiodide of (VII) gave results in agreement with those of Späth and Pailer (*loc. cit.*). The product was a mixture of the neutral, crystalline diene (XI) and a basic substance which was identified through its picrate as regenerated (VII). The ultra-violet absorption spectrum of the diene is consistent with the conjugated structure assigned to it by Späth and Pailer.

Hydrogenation of (VII) gave des-*N*(*a*)-emetineoctahydrobismethine (IX), which was lævorotatory ($[\alpha]_D$ −5°). This base had been obtained previously (Part I) by the Emde degradation of the methochloride of (VI), and was then found to be weakly dextrorotatory ($[\alpha]_D$ +1°), but a repetition of this reaction gave a weakly lævorotatory product ($[\alpha]_D$ −2°). As no crystalline derivatives could be obtained, further comparison of the different preparations was difficult. Since no fresh asymmetric centre is produced in the reduction, it seems very probable that the material obtained by the hydrogenation of (VII) is pure, and that obtained by the Emde degradation is contaminated with a variable amount of a dextrorotatory impurity.

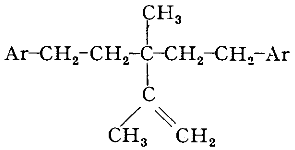
Exhaustive methylation of (IX) gave rise to the nitrogen-free product (X) already described in Part I, together with regenerated (IX). Ozonolysis of (X) gave formaldehyde and a carbonyl compound which has not been completely characterised, but which is not an aldehyde. (IX) therefore contains the structure 

or less probably 

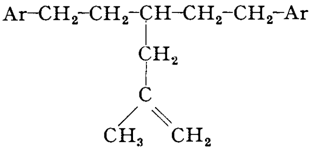
. The substance (X) was optically inactive, within the limits of the experimental error, suggesting that $C_{(11)}$ is the sole remaining asymmetric centre in (IX). There are three possible symmetrical structures for (X) consistent with the accumulated evidence, namely (X*a*), (X*b*), and (X*c*). Allowing for the attachment of N(*b*) to either $C_{(12)}$ or $C_{(11)}$, six possible structures for emetine become apparent, (I*a*) and (I*c*) derived from (X*a*), and four other structures derived in an analogous manner from (X*b*) and (X*c*). A decision between these was reached by a study of the dehydrogenation of des-*N*(*a*)-emetinehexahydromethine (VI).



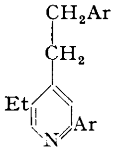
(X*a*.)



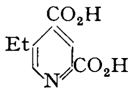
(X*b*.)



(X*c*.)



(XIV.)



(XV.)

When the base (VI) was heated with palladised charcoal at 250—270°, it was largely dehydrogenated, with accompanying demethylation, to give the *pyridine* base (XIV), which was readily separated from unchanged (VI) by virtue of its more weakly basic character. Oxidation of this base with concentrated nitric acid gave an acid, $C_9H_9O_4N$, which was proved to be 5-*ethylpyridine*-2 : 4-*dicarboxylic acid* (XV) by its further oxidation with permanganate to berberonic acid, and by its decarboxylation to 3-ethylpyridine. The possibility of a molecular rearrangement occurring during the dehydrogenation was unlikely at the temperature employed, and was discounted by the successful dehydrogenation of (VI) by aqueous silver acetate at 180°. Under these mild conditions, some of the pyridine base (XIV) was produced directly, but the principal product was the related *N*-methylpyridinium salt, which was converted into (XIV) by thermal decomposition of the chloride. The foregoing degradation shows both the presence of an ethyl group attached to $C_{(11)}$, and the 6-membered nature of ring D, and in association with the other evidence presented above it conclusively proves that emetine possesses the structure (I*a*).

EXPERIMENTAL.

N-*Methylemetinemethine Dimethiodide.*—A solution of *N*-methylemetienmethine (1·33 g.) in ether (12 c.c.) and methyl iodide (1·5 c.c.) was kept at room temperature for 24 hours, and the amorphous precipitate (1·73 g.) was collected. It crystallised in contact with ethylene dichloride, and after recrystallisation twice from acetone formed colourless prisms, m. p. 151—153°, which were dried at room temperature for 2 hours over phosphoric oxide in a vacuum (Found : C, 48·6; H, 6·4; N, 3·1. Calc. for $C_{34}H_{52}O_4N_2I_2,2H_2O$: C, 48·4; H, 6·7; N, 3·3%). Karrer (*Ber.*, 1916, **49**, 2057) described this salt as amorphous.

A solution of the dimethiodide (0·066 g.) in diethyl ketone (5 c.c.) was heated at 100—110° for 3 hours whilst nitrogen was passed through the solution and into a trap containing dilute hydrochloric acid. The contents of the trap were evaporated to dryness and the residue was treated with aqueous sodium hydroxide. Air was aspirated through the solution and into ethereal picric acid, whereupon trimethylamine picrate (3 mg.) was formed, which after crystallisation from alcohol had m. p. and mixed m. p. 217—218°. From the diethyl ketone solution, only dark tarry products were obtained.

Oxidation of Des-N(a)-*emetinetetrahydromethine* (IV).—The base (1·5 g.) was oxidised with barium permanganate as described previously (Part I, *loc. cit.*) and the products were examined by a modified procedure. After the aqueous alkaline solution of the products had been freed from manganese dioxide by filtration, and from neutral and basic matter by extraction with ether, it was rendered acid to Congo-red with sulphuric acid. The precipitated barium sulphate was digested at 100° for 30 minutes and removed by filtration (" Filtercel "). The filter-cake was thoroughly extracted with boiling water (total, 400 c.c.), and the combined aqueous solutions were concentrated to 200 c.c. Extraction 5 times with ether (total, 600 c.c.) removed crude 6-ethylveratric acid (0·362 g.).

The aqueous solution was treated with a slight excess of aqueous barium hydroxide, and the barium sulphate was removed as before. Evaporation of the solution left the crude amino-acid (V) as a yellow resin. It was esterified by being heated under reflux for 2 hours with absolute methyl alcohol (30 c.c.) and concentrated sulphuric acid (1 c.c.). The solution was poured into dry chloroform (150 c.c.) and dry, finely powdered barium hydroxide (5 g.) was added with shaking. After 10 minutes' shaking, the solids were removed by filtration, and the filter-cake was thoroughly extracted with boiling chloroform (total, 200 c.c.). Evaporation of the filtrate left the methyl ester of (V) as a yellow gum (0·671 g.) which distilled as a pale yellow gum (0·577 g.) under 2×10^{-5} mm. from a bath at 100—110°. This ester was hydrolysed by being heated for 5 hours under reflux with 0·1N-barium hydroxide (20 c.c.). The equivalent of 0·05N-sulphuric acid was added, and the precipitated barium sulphate was removed by filtration. After washing of the filter-cake with boiling water (total, 200 c.c.) the filtrate was extracted with ether which removed a trace of gum (2 mg.). Concentration of the aqueous solution yielded the amino-acid (V) as colourless prisms (0·427 g., 40%), m. p. 218—221° with darkening. This m. p. was unchanged by 2 further crystallisations from water. The material was dried over phosphoric oxide in a vacuum at 110° for 2 hours but still appeared to be hydrated (Found : C, 62·1; H, 8·15; N, 3·5. $C_{19}H_{29}O_4N,2H_2O$ requires C, 61·5; H, 9·0; N, 3·8%). Accordingly, the *ethyl* ester was prepared by heating the pure amino-acid (0·074 g.) with alcohol (5 c.c.) and concentrated sulphuric acid (0·2 c.c.) under reflux for 3 hours. The ester was isolated by the procedure described above; it distilled at 120° (bath)/4×10^{-3} mm. as a colourless gum (Found : C, 69·2; H, 8·95; N, 4·2. $C_{21}H_{33}O_4N$ requires C, 69·4; H, 9·15; N, 3·9%).

Des-N(a)-*emetinehexahydromethine* (VI).—Des-*N*(*a*)-emetinetetrahydromethine (4·37 g.), recovered from its pure perchlorate, was dissolved in glacial acetic acid (30 c.c.) and shaken with hydrogen and platinic oxide (0·1 g.); absorption of hydrogen (1·04 mols.) ceased after 20 minutes. The filtered solution was evaporated to dryness, and the residual gum was dissolved in water, treated with excess of aqueous sodium hydroxide, and extracted 4 times with ether. Evaporation of the dried extract gave *des*-N(a)-*emetinehexahydromethine* as a gum (4·38 g.) which crystallised from light petroleum (b. p. 40—60°) as rosettes of colourless needles (3·96 g.), m. p. 78—79·5°. The m. p. was raised to 79—80·5° by distillation at 140° (bath)/2×10^{-5} mm., followed by crystallisation from light petroleum. The substance was dried over phosphoric oxide in a vacuum at 56° for 1 hour (Found: C, 74·45; H, 9·5; N, 3·05, 2·95. $C_{30}H_{45}O_4N$ requires C, 74·5; H, 9·4; N, 2·9%).

A solution of the foregoing base (0·106 g.) in methyl alcohol (1 c.c.) and methyl iodide (2 c.c.) was heated under reflux for 12 hours. Evaporation left a gum, which was dissolved in the minimum volume of hot alcohol, and the solution was poured into aqueous sodium hydroxide. The resulting suspension was extracted thrice with ether and thrice with chloroform. The ethereal extract contained a trace of basic material. Evaporation of the dried chloroform extract left a colourless resin (0·137 g.) which crystallised from aqueous alcohol as short prisms (0·132 g.), m. p. 123—125°, converted by drying at 110° and recrystallisation from anhydrous acetone into the methiodide monohydrate, m. p. 169—170°, alone or in admixture with the salt described in Part I.

Des-N(a)-*emetinehexahydrobismethine* (VII).—A solution of des-*N*(*a*)-emetinehexahydromethine methiodide (4·05 g.) in warm 50% aqueous alcohol was stirred with silver oxide (from 2 g. of silver nitrate) for 45 minutes. The filtered solution (" Filtercel ") was evaporated to dryness, and the residual quaternary hydroxide was decomposed by being heated at 100° under 10 mm. for 2 hours. Ether and water were added to the product, which dissolved completely; the aqueous layer was evaporated to dryness, and the residue was heated as before and again partitioned between ether and water. The aqueous phase was further extracted thrice with ether. Evaporation of the combined ethereal solutions left a clear yellow gum (3·43 g.) which was treated with N-hydrochloric acid (7·5 c.c.), and sufficient water was added to dissolve the salt. After extraction with ether to remove a brown neutral gum (0·097 g.), the aqueous solution was made alkaline to phenolphthalein with aqueous sodium hydroxide. The liberated bases were extracted with 4 portions of ether and were obtained by evaporation of the ethereal solution as a yellow gum (2·75 g.). The aqueous solution was shaken with 4 portions of chloroform, the dried extract on evaporation leaving a brown gum (0·322 g.).

Distillation of the basic product at 155—160° (bath)/5×10^{-4} mm. afforded a pale yellow, viscous gum, which was treated with picric acid (1 equivalent) in alcoholic solution. The *des*-N(a)-*emetinehexahydrobismethine picrate* separated as rosettes of yellow needles (3·48 g., 74%), m. p. 158—159° after slight sintering. This m. p. was raised to 159—160° by repeated crystallisation from alcohol; the final sample was dried at 100° over phosphoric oxide in a vacuum for 2 hours (Found: C, 60·9; H, 6·9; N, 7·6. $C_{31}H_{47}O_4N,C_6H_3O_7N_3$ requires C, 61·15; H, 6·95; N, 7·7%). *Des*-N(a)-*emetinehexahydrobismethine*, recovered from the pure picrate, distilled at 150° (bath)/10^{-5} mm., as a colourless gum (Found: C, 74·6, 74·9; H, 9·4, 9·1; N, 3·0. $C_{31}H_{47}O_4N$ requires C, 74·8; H, 9·5; N, 2·8%), $[\alpha]_D^{20}$ $+5{\cdot}2° \pm 0{\cdot}3°$ (*c*, 3·19 in alcohol). Hydrogenation: 20·2 mg. in glacial acetic acid (platinic oxide) absorbed 1·02 ml. (1·04 mol.) of hydrogen at 15°/754 mm.; reduction was complete in 20 minutes. Ultra-violet absorption spectrum in alcohol: Maximum at 2650 A. (ε, 12,600), inflexion at 3030 A. (ε, 3,560).

The gum obtained from the chloroform extract above was partitioned between water and ether, and the ethereal layer left a brown gum (0·244 g.) on evaporation. Distillation at 140—150°(bath)/5×10^{-4} mm. afforded a yellow gum (0·221 g.) which was treated with picric acid (0·102 g.) in alcohol. A small quantity of the picrate of (VII) (0·026 g.) separated, having m. p. 154—156° after sintering. The mother-liquor was concentrated to small volume and, after removal of the excess of picric acid, the remaining substances were separated into neutral (0·198 g.) and basic (0·01 g.) fractions. After being distilled twice at 150° (bath)/3×10^{-5} mm. the neutral fraction was a pale yellow gum (Found: C, 76·9; H, 9·0; N, 0·0. $C_{29}H_{40}O_4$ requires C, 76·9; H, 8·9%). Ultra-violet absorption in alcohol: Maximum at 2655 A. (ε, 16,100) and inflexion at 3040 A. (ε, 6,160). Microhydrogenation of this *substance* did not give consistent results and was not investigated further. It was oxidised rapidly by permanganate in aqueous acetone.

The mother-liquors from the picrate of (VII) were concentrated and freed from picric acid, and the remaining material was separated into neutral (0·101 g.) and basic (0·25 g.) fractions. The latter, which did not yield a crystalline picrate, was crystallised from light petroleum (b. p. 40—60°) and had m. p. 75—76°, raised to 78—79·5° by distillation at 120°(bath)/10^{-4} mm., followed by crystallisation from light petroleum. In admixture with (VI) the m. p. was 79—80°.

Stability of Des-N(a)-*emetinehexahydrobismethine Methiodide.*—A solution of the hexahydrobismethine base (0·123 g.) in alkali-free ether (5 c.c.) and methyl iodide (0·5 c.c.) was kept at room temperature for 94 hours. The amorphous methiodide (0·154 g., 98%) was washed thoroughly with ether; it could not be induced to crystallise. This salt (0·085 g.) was heated under reflux with water for 3 hours, a slow stream of nitrogen being passed through the solution and into a trap containing dilute hydrochloric acid. Evaporation of the contents of the trap left only a trace of material, which did not contain trimethylamine hydrochloride. Extraction of the aqueous solution of the methiodide 3 times with ether removed only a trace of reddish-brown gum (2 mg.).

Oxidation of Des-N(a)-*emetinehexahydrobismethine* (VII).—The base (0·867 g.), recovered from the pure picrate, was dissolved in purified acetone (50 c.c.), and water (50 c.c.) was added. Aqueous barium permanganate (123·8 c.c., equiv. to 4·1 O) was added to this solution during 11 hours in the manner previously described (Part I, *loc. cit.*); the products were examined by the procedure reported above for the oxidation of the tetrahydromethine. The non-acidic fraction was a brown gum (0·475 g.) and the crude acidic fraction, extracted by ether, was a light-brown crystalline substance (0·136 g.). Recrystallisation of the latter from water (charcoal) yielded 6-ethylveratric acid (0·086 g.), m. p. 141—142°, undepressed on admixture with a synthetic specimen.

After removal of inorganic matter, the original aqueous solution, containing the water-soluble acids and amino-acids, was evaporated to dryness to leave a resin (0·28 g.). Esterification by the method described above and distillation at 100—110° (bath)/8×10^{-5} mm. gave the *methyl* ester of (VIII) as a clear yellow gum (0·181 g.). A portion was redistilled twice for analysis (Found: C, 69·1; H, 9·8; N, 4·0. $C_{21}H_{35}O_4N$ requires C, 69·0; H, 9·7; N, 3·8%).

Hydrolysis of this ester (0·11 g.) by 9 hours' heating with 0·1N-barium hydroxide (20 c.c.) yielded the amino-acid (VIII) which could not be crystallised.

Hofmann Degradation of Des-N(a)-*emetinehexahydrobismethine* (VII).—A solution of the base (0·472 g.) in dry ether (10 c.c.) and methyl iodide (1 c.c.) was kept at room temperature for 60 hours. The ethereal solution was then decanted and the amorphous methiodide was washed with ether, dissolved in 50% aqueous alcohol (20 c.c.), and stirred at 50° for 1 hour with silver oxide (from 0·5 g. of silver nitrate). After filtration ("Filtercel") the solution was evaporated to dryness and the residue was decomposed by being heated at 180—200° (bath)/0·1 mm. for 1 hour. The products distilled at 180° (bath)/4×10^{-3} mm. as a pale yellow gum, and were separated into neutral (0·239 g.) and basic (0·137 g.) fractions. The basic material (0·051 g.) was treated with picric acid (1 equivalent) in alcohol to afford the picrate (0·066 g.), m. p. 158—159°, undepressed on admixture with the picrate of (VII).

The neutral material crystallised from light petroleum (b. p. 40—60°) as rosettes of colourless needles (0·142 g.), m. p. 66—67·5° after sintering at 64°. After being recrystallised from the same solvent, distilled at 130—140° (bath)/8×10^{-5} mm., and recrystallised, it had m. p. 69—70° after slight sintering (Späth and Pailer, *loc. cit.*, gave m. p. 70—72°). Before analysis, the substance was dried at 35° for 2 hours in a vacuum over phosphoric oxide (Found: C, 76·2; H, 8·9. Calc. for $C_{29}H_{40}O_4$: C, 76·9; H, 8·9%). The substance became yellow on storage, and a deep-yellow sample contained C, 74·6; H, 9·2%. Ultra-violet absorption spectrum in alcohol: Maxima at 2280 A. (ε, 24,800) and 2910 A. (ε, 19,100).

Des-N(a)-*emetineoctahydrobismethine* (IX).—The hexahydrobismethine (3·28 g.), regenerated from the pure picrate, was dissolved in glacial acetic acid (30 c.c.) and hydrogenated (platinic oxide) at 16°/768 mm.; absorption of hydrogen (1·05 mols.) was complete in 20 minutes. The filtered solution was evaporated to dryness and the residue dissolved in water and made strongly alkaline with aqueous sodium hydroxide. Extraction thrice with ether (total, 200 c.c.) and evaporation of the dried extract yielded des-*N*(*a*)-emetineoctahydrobismethine (3·26 g.) which distilled at 180° (bath)/5×10^{-6} mm. as a colourless gum, $[\alpha]_D^{13\cdot5}$ $-5{\cdot}0° \pm 0{\cdot}2°$ (*c*, 2·45 in alcohol). Attempts to prepare crystalline salts of this base with picric, perchloric, and hydriodic acid were unsuccessful.

Hofmann Degradation of Des-N(a)-*emetineoctahydrobismethine* (IX).—A solution of the base (3·7 g.) and methyl iodide (3 c.c.) in dry ether (50 c.c.) was kept for 46 hours at room temperature. The methiodide separated as a yellow gum. The ethereal solution was decanted and the gum washed with ether; evaporation of the combined ethereal solutions left a negligible residue. The methiodide was treated with silver oxide (from 4 g. of silver nitrate) in the manner previously described, and the resulting methohydroxide was decomposed by being heated at 150° (bath)/0·2 mm. for 1 hour, followed by distillation at 180° (bath)/2×10^{-5} mm. The resulting pale yellow gum was separated into neutral (0·78 g.) and basic (2·68 g.) fractions. The latter was again subjected to exhaustive methylation in a similar fashion, save that the methohydroxide was heated at 100° (bath)/15 mm. for 2 hours before the products (2·606 g.) were distilled. Again the neutral matter (1·237 g.) was separated, the remaining fraction (1·339 g.) being basic. Distillation of the combined neutral fractions at 180° (bath)/2×10^{-5} mm. yielded the *product* as a pale yellow gum (Found : C, 76·5; H, 9·15; N, 0·0. $C_{29}H_{42}O_4$ requires C, 76·8; H, 9·3%). An alcoholic solution was optically inactive within the experimental error. Hydrogenation: 30·8 mg. in glacial acetic acid (platinic oxide) absorbed 1·64 ml. (1·00 mol.) at 17°/749 mm.; reduction was complete in 12 minutes.

Ozonolysis of the Neutral Substance (X).—A solution of the foregoing substance (0·852 g.) in ethyl chloride (15 c.c.) was cooled to −78° whilst ozonised oxygen (1,440 c.c. of 3·51%; 1·2 mols.) was led in during 24 minutes. The solvent was evaporated and the residue was heated under reflux for 5 minutes with water (20 c.c.) to which silver nitrate (0·015 g.) and zinc dust (0·2 g.) had been added. A slow stream of nitrogen was passed through the solution and into a trap containing an aqueous-alcoholic solution of dimedone. The reflux condenser was then removed and water was distilled slowly from the mixture into the dimedone solution for 30 minutes, with the nitrogen stream still passing. After the addition of more water (20 c.c.) the reaction mixture was heated under reflux for a further 30 minutes, and then the condenser was again removed to allow slow distillation of water into the trap for 30 minutes. The solid which had separated in the trap was collected, washed with water, and dried (0·184 g., 33%); it had m. p. 180—184°. Crystallisation twice from aqueous alcohol raised the m. p. to 188—189°, undepressed on admixture with the dimedone derivative of formaldehyde.

The aqueous suspension of the non-volatile products was shaken thrice with ether, and the combined ethereal extracts were filtered and shaken thrice with aqueous 10% sodium carbonate (total 60 c.c.). Evaporation of the ethereal solution and distillation of the residue at 140—150° (bath)/5×10^{-6} mm. yielded a pale yellow gum (0·637 g.). Attempts to prepare the semicarbazone, 2 : 4-dinitrophenylhydrazone and *p*-nitrophenylhydrazone of this substance afforded sparingly soluble, amorphous products. It did not reduce ammoniacal silver nitrate, and gave no coloration with Schiff's reagent, and only a faint yellow colour with a solution of dianisidine in glacial acetic acid (F. Feigl, " Qualitative Analysis by Spot Tests," 3rd Edition, New York, 1946, p. 340).

*Palladium Dehydrogenation of Des-*N(a)*-emetinehexahydromethine* (VI).—An intimate mixture of the base (0·599 g.) and 10% palladised charcoal (0·5 g.) was heated in a stream of carbon dioxide, the temperature being raised from 250° to 270° during 45 minutes, and maintained at 270° for a further 2 hours. The evolved gases, collected over 50% aqueous potassium hydroxide, occupied 50 c.c. at 20°/750 mm. (1·65 mols.). In all, 10 similar dehydrogenations of the hexahydromethine (total, 6·71 g.) were carried out. The combined products were dissolved in alcohol and freed from catalyst by filtration (" Filtercel "). Evaporation of the alcohol left a brown gum (4·72 g.) which was dissolved in ether (2·4 l.) and shaken with 3 portions of M/50-aqueous citric acid (800, 400, and 200 c.c.). The strong bases thus extracted were recovered in the usual manner as a light-brown gum (1·42 g.) which was crystallised from light petroleum (b. p. 40—60°) to give recovered hexahydromethine (0·992 g.), m. p. 74—76° (mixed m. p. with the original base, 77—79°).

The ethereal solution above, containing the neutral products and weak bases, was shaken twice with 2N-hydrochloric acid (total, 240 c.c.), and the ethereal layer, after being shaken once with 2N-sodium carbonate and once with water, was concentrated to *ca.* 150 c.c. After extraction thrice with 2N-hydrochloric acid (total, 120 c.c.), followed by washing with 2N-sodium carbonate and with water, evaporation of the ethereal layer yielded the neutral matter as a cloudy brown gum (0·696 g.), which was not further investigated. The weakly basic fraction, a clear brown gum (2·41 g.) was recovered from the combined hydrochloric acid extracts in the usual way. Treatment with picric acid (1·3 g.) in alcohol gave a crude picrate (3·12 g.), m. p. 103—106° after sintering. Recrystallisation from ethyl acetate gave the *picrate* (2·49 g., 30%), m. p. 123—124°, of the pyridine base (XIV) as rosettes of yellow needles. Crystallisation thrice from ethyl acetate raised the m. p. to 124·5—126°. A sample for analysis was dried for 2½ hours at 100° in a vacuum over phosphoric oxide (Found : C, 60·95; H, 6·0; N, 8·0. $C_{29}H_{37}O_4N,C_6H_3O_7N_3$ requires C, 60·65; H, 5·85; N, 8·1%). The *pyridine* base (XIV), recovered from the pure picrate, distilled at 160—170° (bath)/8×10^{-5} mm. as a colourless gum, which crystallised from ether as rosettes of colourless needles, m. p. 101·5—102·5°, raised to 102—102·5° by recrystallisation twice from ether. For analysis, it was dried at 78° for 2 hours in a vacuum over phosphoric oxide (Found : C, 74·9; H, 8·05; N, 3·3. $C_{29}H_{37}O_4N$ requires C, 75·15; H, 8·05; N, 3·0%). This base was stable to permanganate in aqueous acetone at room temperature. On hydrogenation, absorption of hydrogen was slow and continued beyond that corresponding to 3 moles, evidently owing to hydrogenation of the benzene rings. Ultra-violet absorption spectrum in methyl alcohol: Maximum at 2880 A. (ε, 11,750). In comparison, 2-*p*-methoxyphenylpyridine showed maxima at 2820 A. (ε, 16,870) and 2600 A. (ε, 14,490).

*Dehydrogenation of Des-*N(a)*-emetinehexahydromethine* (VI) *with Silver Acetate.*—A mixture of the base (1 g.) and silver carbonate (1·72 g., 3 mols.) was dissolved in glacial acetic acid (2·4 g.) and water (15 c.c.), and the solution was sealed in a Carius tube and heated at 180° for 7½ hours. The brownish-red solution was filtered, the filter-cake washed thoroughly with hot water, and the filtrate made alkaline with aqueous sodium hydroxide. Extraction with ether removed the neutral and basic substances, obtained as a brown gum (0·545 g.) by evaporation of the extract. The aqueous solution was acidified with hydrochloric acid, filtered, and evaporated to dryness. The residue was treated with alcohol, and, after filtration to remove sodium chloride, the solution was evaporated to leave the quaternary salts as a brown resin (0·401 g.). A test sample dissolved readily in water, and the solution remained clear on the addition of sodium hydroxide. The remainder of the quaternary matter was decomposed by being heated at 180° (bath)/0·1 mm. for 30 minutes, and the product distilled at

180° (bath)/5 × 10^{-4} mm. as a yellow glass. It was freed from a trace of quaternary material by shaking its ethereal solution with aqueous sodium hydroxide and then with water. Evaporation of the dried ethereal layer left a yellow glass (0·162 g.) which was treated with picric acid (0·078 g.) in methyl alcohol to give a crude picrate (0·203 g.), m. p. 110—112° after sintering at 104°. Crystallisation twice from ethyl acetate gave the picrate, m. p. 124—125°, of (XIV) (mixed m. p. with the foregoing product, 124—125·5°).

The weak bases (0·125 g.) were isolated from the neutral and basic fraction as described in the previous section, and on treatment with picric acid yielded a further quantity (0·077 g.) of the same picrate, m. p. 104—107° after sintering, raised to 124—125·5° after crystallisation twice from ethyl acetate.

Oxidation of the Pyridine Base (XIV).—The base (0·5 g.) was added in portions to concentrated nitric acid (5 c.c.), and the dark solution was warmed gently to start the reaction. When the vigorous reaction had subsided, further quantities of base (0·5 g.) and acid (5 c.c.) were added. After being heated at 100—110° for 3 hours, the solution was evaporated to dryness and the residue, a yellow glass, was treated with concentrated nitric acid (5 c.c.) and heated at 135° for 1 hour. The solution was evaporated on the water-bath, the residue being heated until brown fumes ceased to be evolved. Concentrated nitric acid (2 c.c.) was added and the process repeated 3 times more. The product was finally evaporated to dryness with water (10 c.c.), and the residual gum was again dissolved in water (10 c.c.). Crystallisation ensued to give a pale yellow solid (0·262 g.), m. p. 235—240° (decomp.), which was washed once with boiling ether (10 c.c.) and crystallised from water to give 5-*ethylpyridine*-2 : 4-*dicarboxylic acid* (XV) (0·172 g., 40%), m. p. 237—238° (decomp.). Recrystallisation from glacial acetic acid gave rosettes of colourless needles, m. p. 241—242° (decomp.), unchanged by further crystallisation from glacial acetic acid or water. The product was dried at 100° for 3 hours over phosphoric oxide in a vacuum (Found : C, 55·4; H, 4·35; N, 7·3. $C_9H_9O_4N$ requires C, 55·4; H, 4·65; N, 7·2%). It gave an orange colour with aqueous ferrous sulphate, identical with that given by berberonic acid under the same conditions.

Degradation of 5-*Ethylpyridine*-2 : 4-*dicarboxylic Acid* (XV).—(a) *Oxidation.* A solution of the dicarboxylic acid (0·06 g.) in water (10 c.c.) was heated on the water-bath with potassium permanganate (0·204 g., equiv. to 4·2 O) until the purple colour disappeared (2½ hours). The solution was filtered, the filter-cake was washed with hot water, and the filtrate was concentrated to 10 c.c. To this solution, which was faintly alkaline to phenolphthalein, was added an excess of aqueous silver nitrate; the white precipitate was collected, washed with water, and dried (0·137 g., 90%). It was dissolved in dilute nitric acid (10 c.c. of N/5) and treated with hydrochloric acid (1 c.c. of 2N.). After removal of silver chloride by filtration (" Filtercel ") the solution was evaporated to dryness, and the residue was crystallised from water as plates or prisms (0·042 g., 65%), m. p. 237—238° (decomp.), raised to 241—243° (decomp.) by recrystallisation from water. The m. p. was not depressed on admixture with an authentic specimen of berberonic acid, m. p. 242—243° (decomp.), prepared from berberine (Weidel, *Ber.*, 1879, **12**, 410), and the spacing and intensity of the lines in the powder *X*-ray diffraction photographs of the two specimens were identical.

(b) *Decarboxylation.* The dicarboxylic acid was recovered unchanged after being heated at 150° for 6 hours with glacial acetic acid (1·5 c.c.) in a sealed tube.

A mixture of finely powdered soda-lime (0·15 g.) and the dicarboxylic acid (0·042 g.) was heated in a stream of nitrogen. The temperature was raised from 150° to 400° during 80 minutes, and the issuing gases were bubbled through ethereal picric acid. The temperature was maintained at 400° for 20 minutes. The precipitated picrate was collected, washed with ether, and crystallised from alcohol (charcoal), giving yellow prisms (0·017 g.), m. p. 118—120°. Crystallisation thrice from methyl and ethyl alcohol yielded 3-ethylpyridine picrate, m. p. 125—126° (Prelog, Moor, and Führer, *Helv. Chim. Acta*, 1943, **26**, 846, give m. p. 127°), strongly depressed on admixture with 4-ethylpyridine picrate, m. p. 165—166°.

The *X*-ray examination of berberonic acid was carried out by Dr. C. A. Beevers, University of Edinburgh, and the majority of the absorption-spectrum measurements were made by Dr. A. E. Gillam, University of Manchester, to both of whom we express our sincere thanks. We are grateful to Dr. C. H. Kellaway, F.R.S., for his interest in these investigations, to the Wellcome Foundation Ltd. for generous gifts of emetine, and to the Department of Scientific and Industrial Research for a maintenance grant made to one of us (A. R. B.).

UNITED COLLEGE, UNIVERSITY OF ST. ANDREWS. [*Received, September 8th*, 1949.]